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ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1682 – 1688
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Impact of diabetes mellitus on prognosis of patients infected with hepatitis C virus

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Received 16 October 2006; accepted 10 July 2007

Abstract

Diabetes is a risk factor for the progression of liver fibrosis and development of hepatocellular carcinoma in chronic hepatitis C. However, the impact of diabetes on the long-term prognosis and the synergistic interactions of various host factors for diabetes to the progression of liver fibrosis are unknown. In the present study, we examined the host factors associated with the progression of hepatitis C in 68 patients with a posttransfusion hepatitis (PTH) and analyzed the relationships. Multivariate analysis showed that age of PTH, being male, and type 2 diabetes mellitus were risk factors for the progression of liver fibrosis. By the Kaplan-Meier method, the cirrhosis-free survival rates after the onset of PTH were significantly lower in the diabetic group than in the nondiabetic group ($P < .01$). Diabetes also had a great impact on the long-term prognosis of chronic hepatitis C by reducing the time from PTH to the occurrence of hepatocellular carcinoma ($P < .01$) and to liver-related death ($P < .05$). Coexistence of obesity (body mass index $\geq$25 kg/m^2) or hypertriglyceridemia ($\geq$150 mg/dL) with diabetes had a synergistic effect on liver fibrosis progression in patients with chronic hepatitis C. Thus, the treatment of diabetes, obesity, and hypertriglyceridemia may hold the key to improving the prognosis of chronic hepatitis.

1. Introduction

Chronic infection with hepatitis C virus (HCV) is the leading cause of liver damage. Persistent chronic liver damage eventually progresses from chronic hepatitis to cirrhosis and to hepatocellular carcinoma (HCC) [1-3]. Previous studies have reported that host factors contributing to the progression of chronic hepatitis C to liver fibrosis are age at onset [4,5], sex [5,6], race [7,8], alcohol consumption [9,10], smoking [11], hepatitis B virus coinfection [12,13], HIV coinfection [14,15], complication by hemochromatosis [16], nonalcoholic steatohepatitis [17], schistosomiasis [18] and human leukocyte antigen haplotypes [19].

On the other hand, recent studies have reported that in addition to these host-related factors, the development of diabetes or obesity as a complication is a risk factor for the progression of liver fibrosis and development of HCC in chronic hepatitis C [20-24]. In addition, insulin resistance has been reported frequently in chronic hepatitis C [25]. Recently, Fartoux et al [26] have reported that, through steatosis, insulin resistance is associated with liver fibrosis in chronic hepatitis. However, previous studies were mainly aimed at finding factors related to the degree of liver fibrosis in chronic hepatitis C. Therefore, no studies have sufficiently examined the effects of these factors associated with liver fibrosis on the long-term prognosis, that is, the development not only of cirrhosis and HCC from HCV infection but also of liver-related death. Moreover, synergistic interactions of these factors to the progression of liver fibrosis are still unknown.

In this study, we examined the effects of diabetes and the synergistic factors on the prognosis of HCV infection in patients with a clear onset of posttransfusion hepatitis (PTH).

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doi:10.1016/j.metabol.2007.07.011

2. Methods

2.1. Patients

Fig. 1 shows the design of this study. Of the 839 patients who were admitted to Kanazawa University Hospital and diagnosed with chronic hepatitis C between January 1990 and April 2004, 87 were found to have developed PTH at a definite age on close history taking. These 87 patients were followed periodically for 2 to 46 years with a mean of 20.3 years from the time of the first examination to December 2004. Of these patients, 33 received interferon therapy during the follow-up; and 19 of them achieved a complete response with the disappearance of HCV. Of the 87 patients whose age at onset was known, 68 were included in the study, excluding the 19 patients with a complete response to interferon. Informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Diagnosis of HCV infection and laboratory testing

Blood samples were tested for hepatitis B surface antigen and anti-hepatitis C virus antibodies by commercial immunoassays (Fuji Rebio, Tokyo, Japan). Hepatitis C virus infection was diagnosed by positive serum anti-hepatitis C virus antibodies and liver biopsy histology. The stage of fibrosis was evaluated according to the criteria of Desmet et al [27]. At the first examination, fasting serum lipid levels (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides), glycated hemoglobin (HbA_{1c}), aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, total bilirubin, albumin, prothrombin time, and indocyanine green (ICG) excretion were measured.

2.3. Variables examined

In all 68 patients, the age at onset of PTH, cirrhosis, and HCC, and the age at liver-related death were examined. At the first examination, height, body weight, body mass index (BMI), and the presence or absence of complicating diabetes or hyperlipidemia were examined. *Posttransfusion hepatitis* was defined as hepatitis in which liver function tests showed serum ALT levels to be elevated to more than 2.5 times the reference range between 1 week and 6 months after transfusion. Cirrhosis was diagnosed by histopathologic examination of liver biopsy specimens in 16 of 68 patients. In the remaining patients, cirrhosis was diagnosed by a combination of clinical features of portal hypertension (splenomegaly, ascites, and esophageal varices), biochemical evidence of hepatic failure (percentage of prothrombin time <70%, total bilirubin >2.5 mg/dL, albumin <3.5 g/dL), and abdominal ultrasound and computed tomographic (CT) findings. Hepatocellular carcinomas were detected by imaging modalities such as ultrasound scanning, dynamic CT scanning, magnetic resonance imaging, and abdominal arteriography. Hepatocellular carcinoma was diagnosed by angiographic demonstration of typical hypervascular tumor staining, as well as by typical findings on dynamic CT, such as hyperattenuation areas in the early phase and hypoattenuation areas in the late phase [28]. Liver-*related death* was defined as that associated with liver failure, rupture of esophageal varices, or HCC. To exclude diabetes secondary to cirrhosis, *type 2 diabetes mellitus* was defined as that with a fasting blood glucose level of 126 mg/dL or higher, or with a 2-hour blood glucose level of 200 mg/dL or higher in a 75-g oral glucose tolerance test and an *insulinogenic index*, which is defined as (insulin at 30 min − fasting insulin)/(glucose at 30 min − fasting glucose), of less than 0.4. *Obesity* was defined as a BMI of 25 kg/m^2 or higher, which is defined by the Japan Society for the Study of Obesity, at the first examination. *Hypertriglyceridemia* was defined as a fasting triglyceride level of 150 mg/dL or higher at the first examination. *Hypo–high-density lipoprotein (HDL) cholesterolemia* was defined as a fasting HDL cholesterol level of 40 mg/dL or lower at the first examination.

2.4. Statistical analysis

All serial data were expressed as means ± standard deviations. To identify variables influencing the disease-free survival rate in the period from the onset of PTH to the diagnosis of cirrhosis (*freedom from disease* refers to the absence of a diagnosis of cirrhosis or HCC up to the end of the follow-up or the nonoccurrence of liver-related death), the possibility of type 2 diabetes mellitus, obesity, and hyperlipidemia (hypercholesterolemia, hypertriglyceridemia) being involved was examined by regression analysis using a Cox proportional hazard model. Results of regression analysis were considered significant at $P < .05$ for a given hazard ratio with a 95% confidence interval (CI). Student t test was used to compare initial blood test results between the type 2 diabetes mellitus and nondiabetes groups. Disease-free survival rates in the period from the onset of PTH to the diagnosis of cirrhosis or HCC and to liver-related death were estimated by the Kaplan-Meier method. The influence of type 2 diabetes mellitus on the prognosis of chronic hepatitis C was investigated using the Breslow-Gehan-Wilcoxon

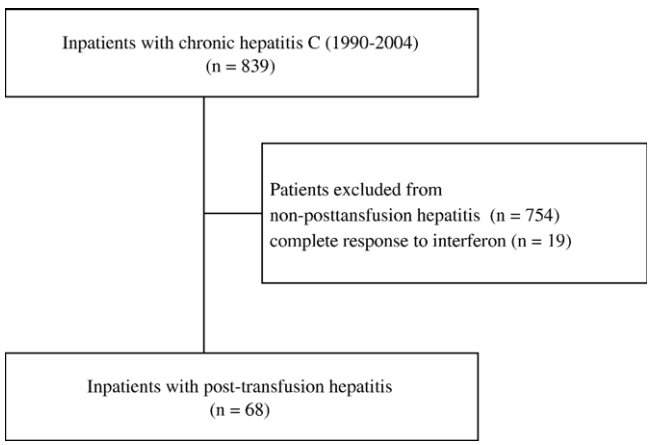

Fig. 1. Study design.

Table 1
Patient characteristics

Sex (male/female)	49/19
Age at onset of PTH (y)	34.6 ± 14.7
IFN therapy (+/−)	14/54
Type 2 diabetes mellitus (+/−)	40/28
BMI (kg/m^2)	23.2 ± 3.5
Obesity (+/−)	17/51
Hypercholesterolemia (+/−)	4/64
Hypertriglyceridemia (+/−/ND)	11/56/1
Hypo-HDL cholesterolemia (+/−/ND)	23/33/12
Alcohol 80 g/d (+/−)	11/57
Diagnosis of liver cirrhosis (+/−)	42/26
Diagnosis of HCC (+/−)	26/42
Occurrence of liver-related death (+/−)	22/46

IFN indicates interferon; ND, not determined.

method. Patients who were diagnosed as being complicated by cirrhosis or HCC at the first examination were analyzed on the assumption that the period from the onset of PTH to the first examination is the disease-free period.

3. Results

3.1. Study population

As shown in Fig. 1, 68 patients with chronic hepatitis C were finally analyzed. The patient characteristics of this group are shown in Table 1. The 68 patients consisted of 49 men and 19 women, with a mean age of 34.6 years at the onset of PTH. Of these patients, 40 were diagnosed as having diabetes as a complication in the period from the onset of PTH to this study; and 28 were not complicated by diabetes. Of 40 patients diagnosed as having diabetes, 31 patients were diagnosed for liver cirrhosis. In the patients, 25 of 31 had been diagnosed for diabetes before they were diagnosed for liver cirrhosis. The mean BMI at the first examination was 23.2 kg/m^2. When obesity was defined as a BMI of 25 kg/m^2 or higher, 17 of the 68 patients were obese. Four patients had hypercholesterolemia, 11 patients had hypertriglyceridemia, and 23 patients had hypo-HDL cholesterolemia. Of the 68 patients, 42 were diagnosed with cirrhosis; and 26 were complicated by HCC. Liver-related death occurred in 22 of the 68 patients between the onset of PTH and the present study. The overall median duration of disease progression to cirrhosis and HCC was 20 and 22 years, respectively.

Table 2
Factors influencing the progression from PTH to cirrhosis

Variables	Hazard ratio	95% CI	*P*
Age at onset of PTH ≥35 y	4.691	2.408-9.140	.001
Sex male	1.269	0.652-2.472	.483
Hypertension	1.378	0.632-2.472	.420
Type 2 diabetes mellitus	2.906	1.377-6.131	.005
Fasting plasma glucose	1.005	1.001-1.009	.007
HOMA-IR	1.065	0.962-1.179	.228
HbA_{1c} (%)	1.211	1.083-1.354	.001
Obesity	2.693	1.371-5.292	.004
BMI	1.106	1.010-5.476	.030
Hypercholesterolemia	2.728	0.408-1.735	.088
Hypertriglyceridemia	2.641	1.274-5.476	.009
Low-HDL cholesterolemia	0.842	0.408-1.735	.640
AST ≥80 IU/L	1.181	0.625-2.225	.608
ALT ≥80 IU/L	0.713	0.354-1.437	.345
Alcohol ≥80 g/d	1.087	0.519-2.275	.825

HOMA-IR indicates homeostasis model assessment of insulin resistance.

Table 3
Factors influencing the progression from PTH to cirrhosis

Multivariate analysis			
Variables	Hazard ratio	95% CI	*P*
Age at onset of PTH ≥35 y	24.542	6.329-95.172	.001
Sex male	8.264	1.962-33.333	.004
Type 2 diabetes mellitus	8.395	2.234-31.541	.002
Obesity	2.168	0.809-5.814	.124
Hypertriglyceridemia	0.257	0.065-1.019	.053
AST ≥80 IU/L	1.473	0.439-4.939	.530
ALT ≥80 IU/L	0.419	0.115-1.528	.188
Alcohol >80 g/d	1.124	0.360-3.512	.841

3.2. Variables associated with progression of liver fibrosis in patients with chronic hepatitis C

Host factors having influence on liver fibrosis during the transition period from PTH to cirrhosis were evaluated by univariate and multivariate analysis. By univariate analysis, the following factors were identified as significantly contributing to the progression of liver fibrosis: onset of PTH at age 35 years or older, type 2 diabetes mellitus as a complication, high fasting plasma glucose, high HbA_{1c}, obesity (BMI ≥25 kg/m^2), high BMI, and hypertriglyceridemia (Table 2). By multivariate analysis, the following factors were identified as significantly contributing to the progression of liver fibrosis: onset of PTH at age 35 years or older, being male, and type 2 diabetes mellitus as a complication (Table 3).

3.3. Diabetes as a risk factor for progression of liver fibrosis

Disease-free survival rates in the period from PTH to cirrhosis in the diabetic and nondiabetic groups were estimated by the Kaplan-Meier method. Posttransfusion hepatitis progressed to cirrhosis in a total of 42 patients, of whom 30 (71.4%) were complicated by diabetes but 12 (28.6%) were not. Table 4 shows disease-free survival rates. The disease-free survival rates 10, 20, and 30 years after the onset of PTH were significantly lower in the diabetic group, at 85.0%, 50.0%, and 25.0%, respectively, than in the nondiabetic group, at 100%, 95.5%, and 43.6%, respectively ($P < .01$) (Table 4A).

Because HbA_{1c} was identified as a factor contributing to liver fibrosis by univariate analysis, the diabetic group was divided into a group with poor glycemic control (HbA_{1c} ≥7.0%) and a group with good glycemic control (HbA_{1c} <7.0%); and the disease-free survival rate was estimated by

Table 4
Disease-free survival rates from PTH to cirrhosis

		10 y	20 y	30 y
Disease-free survival rates for cirrhosis				
A:	DM(+) (n = 40)	85.0%	50.0%	25.0%
	DM(−) (n = 28)	100%	95.5%	43.6%*
B:	DM(+) HbA_{1c} ≥7.0 (n = 24)	95.8%	54.2%	33.3%
	DM(+) HbA_{1c} <7.0 (n = 15)	64.3%	35.7%	7.1%**
C:	DM(+) obesity(+) (n = 27)	72.4%	36.4%	18.2%
	DM(+) obesity(−) (n = 13)	94.2%	72.4%	31.2%*
D:	DM(+) TG(+) (n = 31)	57.1%	14.3%	0.0%
	DM(−) TG(−) (n = 7)	90.3%	50.8%	25.8%*

TG indicates hypertriglyceridemia.
* $P < .01$.
** $P < .05$.

the Kaplan-Meier method (Table 4B). The disease-free survival rates 10, 20, and 30 years after the onset of PTH were significantly lower in the group with poor glycemic control, at 64.3%, 35.7%, and 7.1%, respectively, than in the group with good blood glucose control, at 95.8%, 54.2%, and 33.3%, respectively ($P < .05$).

3.4. Synergistic effect of obesity or hypertriglyceridemia for liver fibrosis progression

Similar to glycemic control, obesity was identified as a significant factor contributing to liver fibrosis progression by univariate analysis. Therefore, disease-free survival rates for a combination of diabetes and obesity were estimated by the Kaplan-Meier method adjusted by sex and onset of PTH. The disease-free survival rates 10, 20, and 30 years after the onset of PTH were significantly lower in the obese diabetic group, at 72.7%, 36.4%, and 18.2%, respectively, than in the nonobese diabetic group, at 94.2%, 72.4%, and 31.2%, respectively ($P < .01$) (Table 4C).

In the same way, the disease-free survival rates were estimated by the Kaplan-Meier method in patients with a combination of diabetes and hypertriglyceridemia, which had been identified by univariate analysis as significant factors contributing to liver fibrosis progression. The disease-free survival rates 10, 20, and 30 years after the onset of PTH were significantly lower in the hypertriglyceridemic diabetic group, at 57.1%, 14.3%, and 0%, respectively, than in the nonhypertriglyceridemic diabetic group, at 90.3%, 50.8%, and 25.8%, respectively ($P < .01$) (Table 4D).

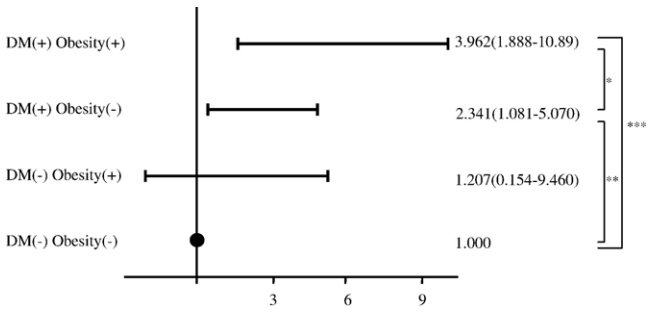

Fig. 2. Hazard ratio of diabetes complicated with obesity for progression to cirrhosis. *$P = .013$, **$P = .031$, and ***$P = .007$. DM indicates diabetes mellitus.

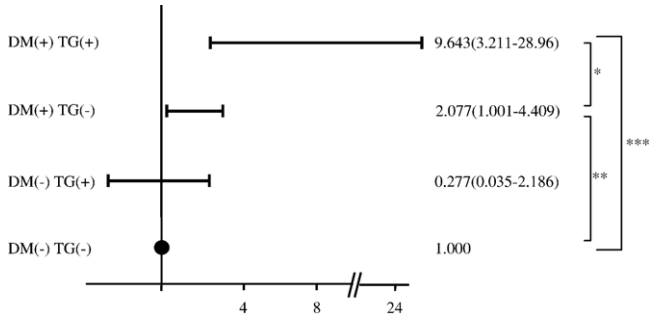

Fig. 3. Hazard ratio of diabetes complicated with hypertriglyceridemia for progression to cirrhosis. *$P = .005$, **$P = .050$, ***$P = .001$. TG indicates hypertriglyceridemia.

Combinations of obesity and diabetes or hypertriglyceridemia and diabetes as risk factors for progression to cirrhosis were analyzed using the Cox proportional hazard model adjusted by sex and onset of PTH. When the risk of nonobese nondiabetic patients was assumed to be 1, the hazard ratio of the nonobese diabetic patients was 2.341 (95% CI, 1.081-5.070; $P = .031$); and the hazard ratio of the obese diabetic patients was 3.962 (95% CI, 1.888-10.89; $P = .007$) (Fig. 2). When the risk of nonhypertriglyceridemic nondiabetic patients was assumed to be 1, the hazard ratio of the nonhypertriglyceridemic diabetic patients was 2.077 (95% CI, 1.001-4.409; $P = .001$); and the hazard ratio of the hypertriglyceridemic diabetic patients was 9.643 (95% CI, 3.211-28.96; $P = .001$) (Fig. 3).

3.5. Diabetes as a risk factor for HCC and liver-related death

In 26 of the 68 patients, HCC developed between the onset of PTH and the present study. We examined the influence of diabetes as a complication on the development of HCC from posttransfusion chronic hepatitis C. The disease-free survival rates 10, 20, and 30 years after the onset of PTH were significantly lower in the diabetic group, at 92.5%, 66.4%, and 40.9%, respectively, than in the nondiabetic group, at 100%, 95.5%, and 81.6%, respectively ($P < .01$) (Table 5A).

Liver-related death occurred in 22 of the 68 patients between the onset of PTH and the present study. We

Table 5
Disease-free survival rates from PTH to HCC and liver-related death

	10 y	20 y	30 y
A: Disease-free survival rates for HCC			
DM(+)	92.5%	66.4%	40.9%
DM(−)	100%	95.5%	81.6%*
B: Disease-free survival rates for liver-related death			
DM(+)	100%	84.1%	49.9%
DM(−)	100%	95.5%	75.8%**

* $P < .01$.
** $P < .05$.

examined the influence of diabetes as a complication on liver-related death after PTH. The survival rates 10, 20, and 30 years after the onset of PTH were significantly lower in the diabetic group, at 100%, 84.1% and 49.9%, respectively, than in the nondiabetic group, at 100%, 95.5% and 75.8%, respectively ($P < .05$) (Table 5B).

4. Discussion

In this study, we retrospectively examined the impact of diabetes as a complication on the natural course of chronic hepatitis C after HCV infection in 68 patients whose age at onset of PTH was known. The effects of diabetes on the long-term prognosis in the patients with HCV infection have not been well characterized because glucose intolerance including diabetes occurs when the liver disease is severe; and therefore, it is difficult to analyze the relationship. The liver is a key organ in glucose homeostasis. In the fasting state, normoglycemia is maintained by hepatic gluconeogenesis. Insulin suppresses hepatic glucose output by inhibiting gluconeogenesis and glycogenolysis. On the other hand, hepatic glucose uptake is generally considered to be passive and independent of insulin action. These are reasons why secondary diabetes due to severe hepatic diseases, such as hepatic failure or liver cirrhosis, is often characterized with relatively lower fasting plasma glucose levels due to the impaired hepatic reserve for gluconeogenesis and postprandial hyperglycemia due to the absolute reduction of liver mass. In contrast, type 2 diabetes mellitus is characterized by the impaired action of insulin to inhibit gluconeogenesis in the liver in the fasting state [29] and impaired early-phase insulin secretion after glucose challenge. In the present study, we focused on primary (type 2 diabetes mellitus) diabetes to examine whether it affects the prognosis of chronic hepatitis C or not. To clarify it, we defined *type 2 diabetes mellitus* as the disease showing high fasting glucose and impaired early-phase secretion of insulin (an insulinogenic index of less than 0.4). According to the criteria, 40 patients were diagnosed for diabetes. Thirty-one of 40 were diagnosed for liver cirrhosis. In the patients, 25 of 31 had been diagnosed for diabetes before they were diagnosed for liver cirrhosis. Therefore, in most cases (about 80%) in the present study, it does not mean that diabetes was caused by severe liver disease.

By univariate analysis, the following factors were identified as contributing to the progression of liver fibrosis after the onset of PTH: onset of PTH at age 35 years or older, type 2 diabetes mellitus a complication, high fasting blood glucose, high HbA_{1c}, high BMI, and hypertriglyceridemia. Many researchers have reported a close relationship between the progression of chronic hepatitis C and the age at onset of HCV infection [4,5]: an older age at infection is considered to be associated with its faster progression. This was in agreement with the finding of this study that the age of 35 years or older was a risk factor for the progression of liver fibrosis in PTH.

Recently, much has been elucidated about the relationship between type 2 diabetes mellitus as a complication and HCV infection [20-22,30-34], including HCV infection itself as a risk for the development of diabetes [30,32,33]. Type 2 diabetes mellitus has also been reported to have an impact on the promotion of liver cirrhosis in chronic hepatitis C [34,35] and has been suspected of not only being a risk for the development of HCC in chronic hepatitis C, but also of being involved in the development of HCC without hepatitis B virus or HCV infection [36,37]. In addition, it has been reported that diabetes accelerates the rate of recurrence of HCC in patients with surgical treatment [38]. In a cross-sectional study of liver biopsy specimens, Monto et al [35] examined the relationship between diabetes and liver fibrosis in terms of the degree of liver fibrosis at the time of liver biopsy. Considering the period from the onset of PTH to the diagnosis of cirrhosis, we estimated the disease-free survival rate by the Kaplan-Meier method and found that diabetes as a complication was a risk factor contributing to the progression of PTH to cirrhosis, which was consistent with the findings of Monto et al. In addition, in this study, the diabetic group with poor glycemic control ($HbA_{1c} \geq 7.0\%$) had a significantly faster progression to cirrhosis than the group with good glycemic control ($HbA_{1c} < 7.0\%$), suggesting the importance of strict glycemic control in patients with chronic hepatitis C complicated by diabetes in delaying its progression to cirrhosis.

Similar to diabetes, obesity was identified by univariate analysis as a risk factor contributing to the progression from the onset of PTH to cirrhosis. In accordance with our results, many researchers reported that obesity was a factor involved in the progression of liver fibrosis [23,24]. In addition, this study showed that hypertriglyceridemia was a factor contributing to the progression of liver fibrosis. To date, no studies have reported a relationship between hypertriglyceridemia and the progression of chronic hepatitis C, leaving the mechanism of hypertriglyceridemia in promoting liver fibrosis unclear. However, hypertriglyceridemia may be associated with insulin resistance as a pathologic state common to diabetes and obesity, which is potentially related to liver fibrosis. Recently, Fartoux et al [26] compared the homeostasis model assessment of insulin resistance and serum insulin levels with liver steatosis and fibrosis, and reported that insulin resistance is a risk factor for steatosis in liver tissue and that high blood insulin levels contribute to the progression of fibrosis through steatosis. In addition, we have experimentally demonstrated that insulin resistance accelerates not only steatosis, but also inflammation and fibrosis, in the liver of a dietary rat model of nonalcoholic steatohepatitis and that therapy focusing on insulin resistance ameliorates the entire pathologic spectrum of steatohepatitis [39].

On the other hand, multivariate analysis identified age at onset of PTH ≥35 years, being male, and type 2 diabetes mellitus as significant factors contributing to the progression of liver fibrosis, but did not identify obesity or hypertriglyceridemia as an independent factor. This is probably because

many of the patients studied were complicated by these diseases. Indeed, diabetic patients are known to be frequently complicated by obesity or hypertriglyceridemia; but the effects of these diseases complicating diabetes on the progression of liver fibrosis have not been elucidated. Therefore, in this study, we examined the impact of obesity or hypertriglyceridemia complicating diabetes on liver fibrosis by comparing the duration of progression of PTH to cirrhosis between the diabetic groups with or without obesity or hypertriglyceridemia. The comparison showed that PTH progressed to cirrhosis significantly faster in the complicated group than in the noncomplicated group. The rates of risk for progression to cirrhosis were 1.692 and 4.643 times higher in diabetic patients complicated with obesity and hypertriglyceridemia, respectively, compared with those in patients with diabetes alone. These results suggest that control of body weight and blood triglyceride in addition to blood glucose is more effective to prevent the progression of liver fibrosis in patients with chronic hepatitis C.

Regarding the impact of diabetes on long-term prognosis of patients with chronic hepatitis C, we examined the temporal influence of diabetes on the occurrence of HCC and liver-related death. The results indicate that diabetes as a complication has a great impact on the long-term prognosis of chronic hepatitis C by reducing the time from PTH to the occurrence of HCC and to liver-related death. Consistent with our results, recent studies have reported that complication of diabetes in chronic hepatitis C is a risk factor for the development of HCC [36,37] and is a prognosis-determining factor after hepatectomy for HCC [40,41]. The conclusions from this study are limited because this nonprospective study could not accurately determine the age at onset of diabetes, cirrhosis, or HCC. However, taken together with previous reports, the results of the present study suggest that the treatment of diabetes, obesity, and hypertriglyceridemia holds the key to improving the prognosis of chronic hepatitis C.

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